Harm Reduction of Cigarettes

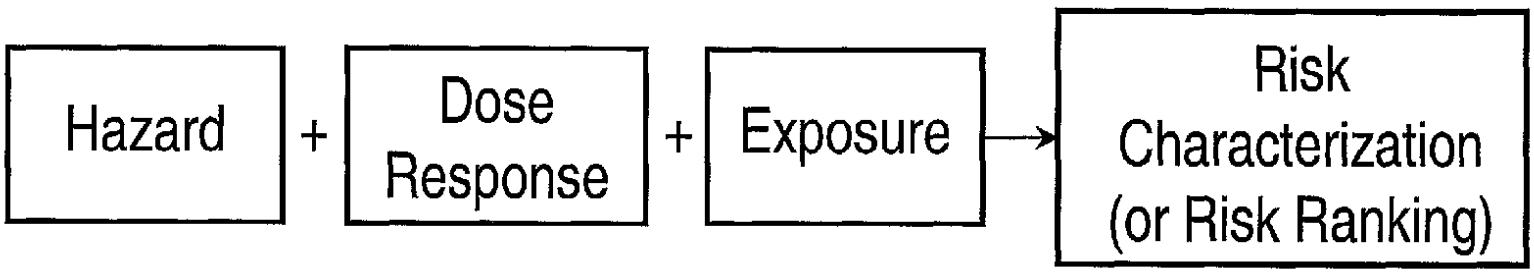
- Philip Morris Takes the Pursuit of Harm Reduction as a Priority
  - There is no safe cigarette
  - We agree that smoking causes lung cancer and other diseases
- We Are Pursuing Harm Reduction in a Responsible Way
- We Welcome the Involvement of the Public Health Community

PM3001168003

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction of Cigarettes

- How Does One Pursue Relevant Harm Reduction Testing?



  - –Results of PM's electrically heated cigarette design

- What Is a Responsible Harm Reduction Evaluation Process?

- Other Philip Morris Activities Toward the Future

PM3001168004

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

How Does One Pursue Relevant Harm Reduction Testing?

PM3001168005

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Hazard

Assays That Are in Use and Validated

- Smoke Chemistry
  - Based on work of IARC, U.S. Consumer Products Safety Commission
- Genotoxicity (Ames)
  - *In Vitro* screen for carcinogenicity
- Cytotoxicity
  - *In Vitro* evaluation of irritancy
- Rat 90-Day Inhalation
  - Whole animal exposure

Handout Provided: *Society of Toxicology Posters and Abstracts, 1998 and 2000*
- Discrimination of Cigarette Mainstream Smoke Condensates with the Salmonella Reverse Mutation Assay
- Discrimination of Cigarette Mainstream Smoke with the Neutral Red Uptake Cytotoxicity Assay
- Equi-Effect Design for Subchronic Inhalation Toxicity Studies Comparing Conventional and Novel Cigarettes
- Toxicological Characterization of a Novel Cigarette Paper
- Effects of the Addition of Flavor Ingredients to the Tobacco on the Chemical Composition and Biological Activity of Cigarette Smoke

PM3001168006

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Hazard

Example of Hazard Evaluation Using Electrically Heated Cigarette

Handout Provided: Society of Toxicology Posters and Abstracts, 1998 and 2000
- Evaluation of an Electrically Heated Cigarette
- The Influence of a Modified Puffing Regimen on the Yields of Smoke Constituents: Electrically Heated and Conventional Research Cigarettes

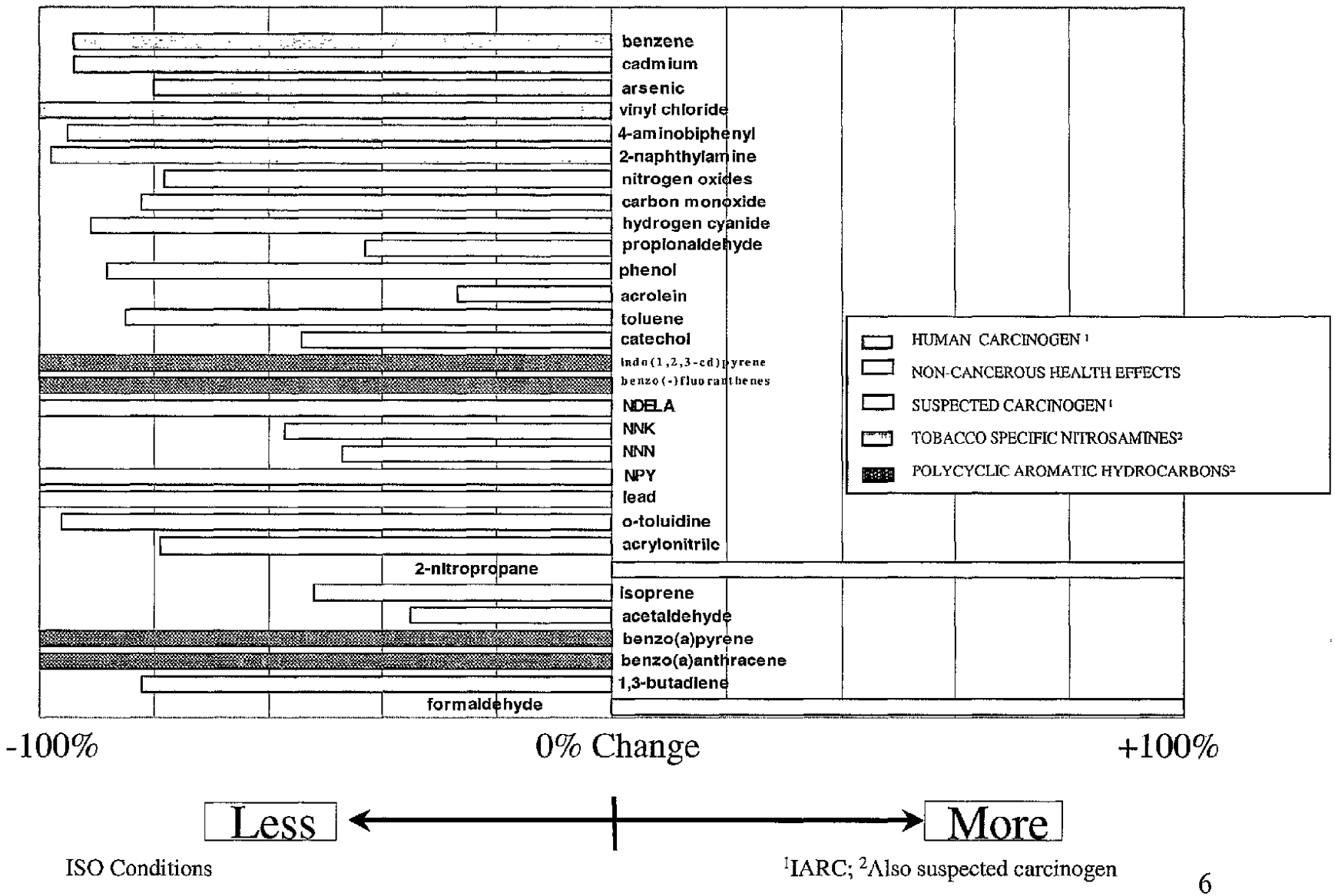
PM3001168007

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Hazard

Electrically Heated Cigarette

Constituent Amounts Compared to an Industry Reference Cigarette (1R4F) (Per mg of TPM)



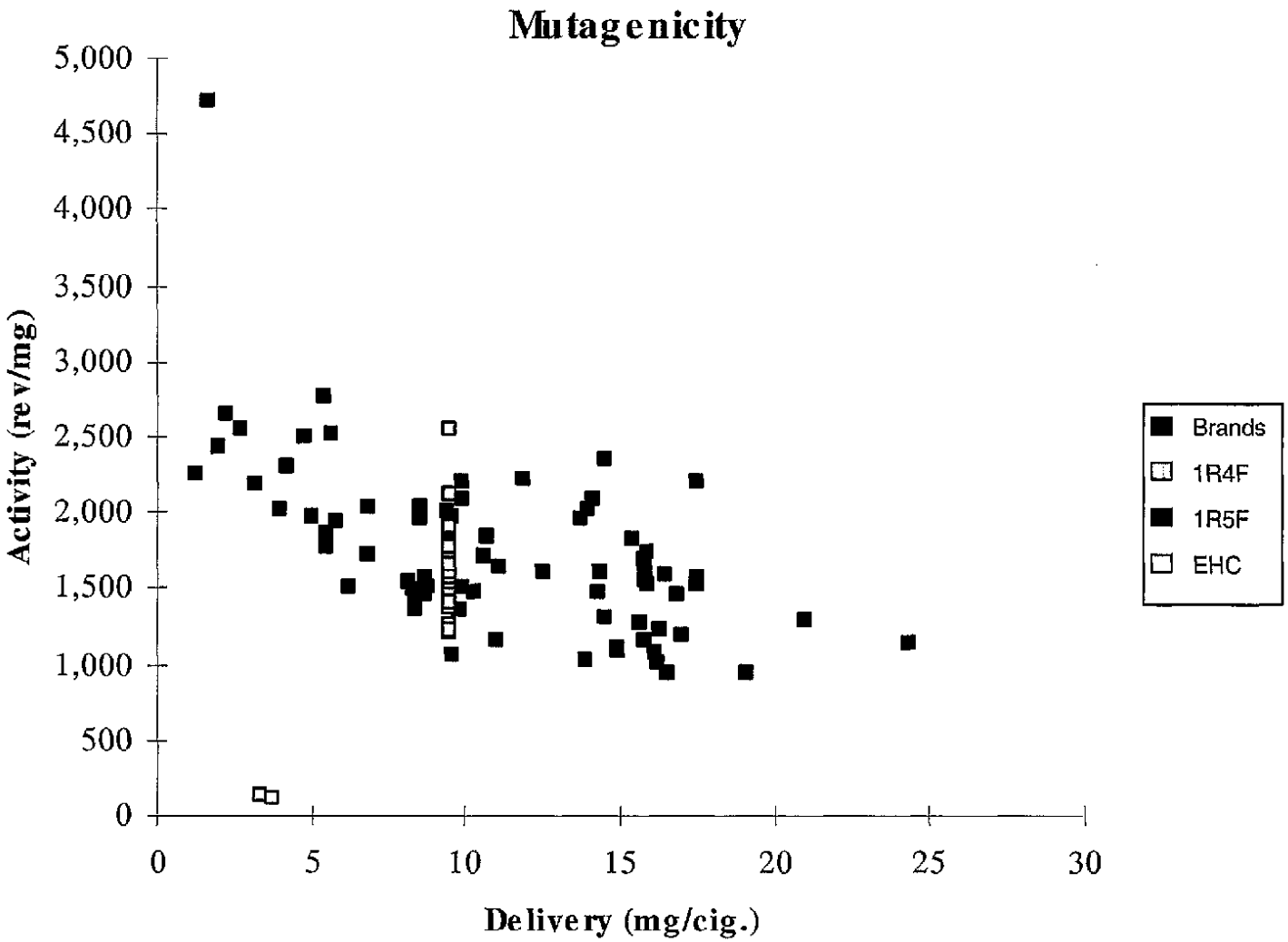
ISO Conditions

[1]IARC; [2]Also suspected carcinogen

PM3001168008

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Hazard
Electrically Heated Cigarette
Ames Assay - Strain TA98 (Per mg TPM)



Steele, *et al.* (1995) Mutation Research, 342: 179-190

PM3001168009

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Hazard

- Results (per mg TPM) (compared to 1R4F reference)
  - Cytotoxicity
    - Decreases
  - Rat 90-Day Inhalation
    - Similar

PM3001168010

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Hazard

Need for Further Assay Development:

- Smoke chemistry, Ames, cytoxicity, and inhalation
  - Data useful for acceptability testing
  - Represents diverse spectrum of assays to evaluate smoke activity
  - incomplete for harm reduction determination
- Surrogate markers suitable to assess harm reduction ideally need to be:
  - mechanistically related to the disease
  - sensitive and dose-responsive
  - reproducible and validated
- However, the scientific community has limited understanding of the relevant pathogenic mechanisms of the diseases
- Therefore, use standardized assays as a default
  - available for carcinogenicity
  - lacking for cardiovascular and chronic obstructive pulmonary diseases
- Started programs to address these assay gaps
  - PM will use such assays in its harm reduction evaluations as these assays become validated

PM3001168011

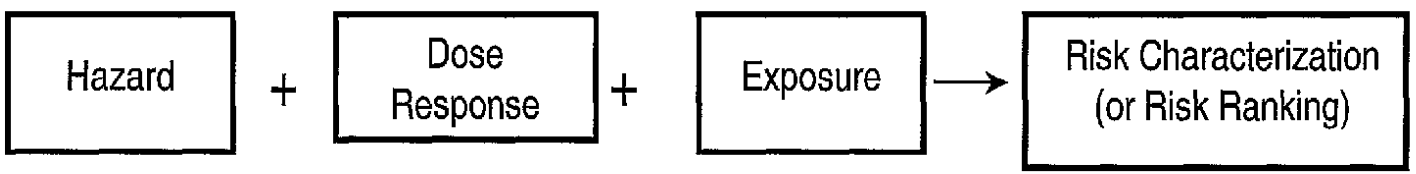
Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Exposure

Machine Cigarette Smoking Compared to Consumer Smoking

- Machine smoking
  - Standardized method allows comparison of hazard testing results
  - Standardized method useful to assure consistency in manufacturing and inter-brand comparison (*e.g.* FTC, ISO)
  - Can provide relative ranking of smoke constituent yields for smoking conditions used

- Consumer smoking
  - Actual exposure to smokers is an integral part of cigarette harm reduction evaluation
  - PM will incorporate such data in its harm reduction evaluation



PM3001168012

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Exposure

Lessons Learned from Low Tar Cigarettes

- Benefits of quitting smoking outweigh those to be gained through reduction in "tar"
- Data are unclear
  - Meta-analysis suggests filters may have reduced relative risks by approximately 40%
  - Lung cancer may have risen faster than expected in the U.S.
  - Lung cancer may have fallen faster than expected in the U.K.
- Compensatory smoking behaviors play a role
- Need data on exposure in order to assess cigarette design changes

PM3001168013

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Exposure

Total Exposure

- To determine the exposure of the U.S. population of adult cigarette smokers to whole cigarette smoke based on suitable biomarkers.
- To investigate whether the smoke exposure of U.S. adult cigarette smokers differs for 4 segments of FTC tar delivery covering the range from 1 to 20 mg.
- Approximately 6,000 adult subjects

PM3001168014

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Exposure
Total Exposure - Current Smoking Population

	Distribution (%)				
	Total	13+mg*	7-12mg*	3-6mg*	0-2mg*
Total	100.0	42.5	43.7	11.1	1.4
Gender					
Male	51.0	59.7	46.7	36.2	29.3
Female	49.0	40.3	53.3	63.8	70.7
Age					
18-24	15.7	17.6	16.4	8.0	0.9
25-34	21.0	21.3	22.8	16.0	2.7
35-44	25.7	26.1	25.8	25.8	17.9
45-54	19.8	19.2	18.8	24.6	27.3
55-64	10.5	9.8	9.7	14.7	23.9
65+	7.2	6.0	6.5	10.9	27.3
Race					
White	80.7	72.9	85.5	89.6	91.9
Black	8.6	14.8	4.4	2.9	2.1
Hispanic	4.0	5.1	3.6	2.0	0.8
Asian	1.2	1.0	1.4	1.0	0.9
Native American	1.4	1.7	1.3	1.1	0.6
Mixed	0.9	1.2	0.9	0.4	0.6
Other	0.8	0.8	0.7	0.7	0.8
Education					
No College	54.0	62.0	49.9	42.5	36.2
Any College	43.6	35.4	47.8	55.6	61.9
Income ($)					
< 10,000	5.6	7.2	4.6	3.5	2.6
10,000 - 19,999	13.2	15.6	11.8	9.4	7.5

Data Source: Philip Morris Tracking Survey

*Per mg tar, as per FTC Protocol

PM3001168015

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Exposure

Total Exposure - Biomarkers of Exposure

BIOMARKER	SAMPLE MATERIAL	SMOKE CONSTITUENT	SMOKE PHASE (b)
Acetonitrile	Exhalate and blood	Acetonitrile	GVP
Carbon monoxide	Exhalate	Carbon monoxide	GVP
Carboxy-hemoglobin	Blood	Carbon monoxide	GVP
Hb adducts of 3- and 4-aminobiphenyl	Blood	3- and 4- aminobiphenyl	PP
Nicotine and nicotine metabolites (a)	24-hr urine	Nicotine	PP
NNAL and NNAL-glucuronide	24-hr urine	NNK	PP
Cadmium	Blood	Cadmium	PP

(a)cotinine, 3-hydroxycotinine, nicotine glucuronide, cotinine glucuronide, and 3-hydroxycotinine glucuronide,
(b)GVP: gas-vapor phase; PP: particle phase

PM3001168016

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Exposure

Total Exposure - Questionnaire

Evaluations:

The following information will be collected from all study subjects:

- Demographics (age, gender, ethnic characterization, marital status, education, socioeconomic status, geographic location);
- Health status and history;
- Exposure to cigarette smoke by active smoking, brands smoked (incl. information on "tar" and nicotine yield (FTC listing), mentholation, filter type, circumference, and cigarette length) for a specified timeframe, daily tobacco consumption;
- Smoking activities during 2 days prior to and during day of urine sample collection (diary);
- Smoking characteristics (e.g., inhalation/puffing);
- Exposure to ETS (strength and duration);
- Occupational exposures (in particular those that could interfere with the selected biomarkers);
- Diet characteristics incl. alcohol consumption;
- Hobbies;
- Home heating systems;
- Exposure to car exhaust;
- Medication/supplementation such as herbal or vitamin supplements (if at least 3 days/week), chemotherapeutics, acetylsalicylic acid-containing drugs, cyclooxygenase inhibitors;
- Start of last menstrual period (women);
- Use of non-tobacco nicotine products;
- Physical activity;
- Smoking activities during 2 days prior to and during day of urine sample collection.

PM3001168017

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Testing - Exposure

ETS Reductions - Accord* *vs.* Merit**

Parameter	Estimated % Reduction
TPM	92.7
UVPM	95.6
FPM	95.6
Solanesol	89.0
Nicotine	98.0
Acetaldehyde	95.5
Isoprene	96.0

- Compounds detected in ETS from Merit but not detected in ETS from Accord:
  - CO
  - 3-ethenyl pyridine
  - Benzene
  - Toluene
  - Fluoranthene
  - Pyrene
  - Chrysene
  - Benzo(a)anthracene
  - Benzo(b)fluoranthene
  - Benzo(a)pyrene

*Electrically Heated Cigarette

** Merit® Cigarette - German Market, 7 mg tar; cigarettes purchased in 2000

PM3001168018

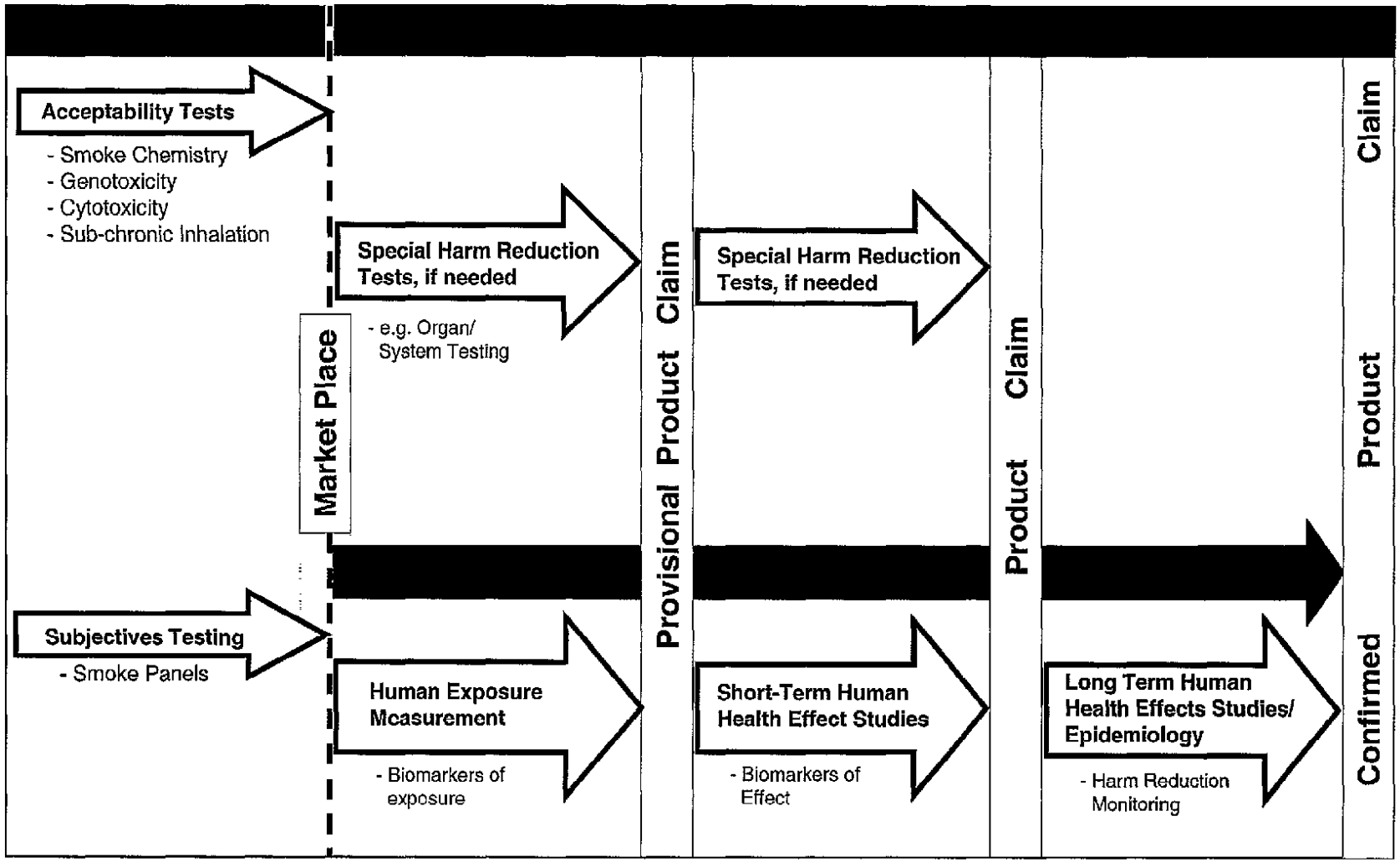
Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

What Is a Responsible Harm Reduction Evaluation Process?

PM3001168019

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Evaluation Process
Proposed Process for Reduced-Harm Product Evaluation



Time for testing, not development

Handout Provided: Institute of Medicine Submissions

Philip Morris Presentation to World Health Organization - Scientific Advisory Committee on Tobacco Product Regulation - October 13, 2000

PM3001168020

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Harm Reduction Evaluation Process

- Harm Reduction Evaluation Process
  - Should be developed with the public health community
  - External scientific review is important
- Should a given reduced harm change be made to all products?
  - If possible, should do so
    - *e.g.* TSNAs in tobacco
      - Should remove if possible
      - Not a likely source of harm
      - TSNA reduction alone is not sufficient data for reduced harm claim
  - Not always possible
    - *e.g.*, electrically heated cigarettes
- How to pursue and responsibly communicate reduced harm products?
  - The Canadian Federal Government has recognized that for those who cannot or will not quit smoking, "*...product modification may have some public health potential*". In addition, the Government has also recognized that "*If smokers would not buy these products, product modification initiatives would fail*". Thus 'harm reduction' is part of the Canadian Government's policy regarding tobacco usage. However "*The federal government's policy objective with respect to tobacco continues to be* ***to reduce tobacco consumption among Canadians and the resultant adverse health effects, to the extent possible***"[1]
  - Cannot do certain technologies on all products
    - consumer choice
    - *e.g.*, electrically heated cigarettes
  - Taste compromise, or ritual change, may otherwise keep smokers from switching
  - How does one address the concern that communication of reduced harm attributes to consumers may have an adverse effect on public health?
    - Use incremental approval (see Reduced Harm Process Chart)
      - Information communicated progresses no further than the science allows
      - Information communicated is discontinued if further testing does not continue to support it
      - Evaluation of the effect of such communication on overall health impact of smoking is addressed
    - Evaluate communications of reduced harm for clarity of message

[1]Report of Canada's Expert Committee on Cigarette Toxicity Reduction - 1998

PM3001168021

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Other PM Activities Toward the Future

- Product Development for Products Worldwide
  - Electrically Heated Cigarette--further improvements
  - Banded Paper for reducing ignition propensity
  - New potential reduced harm designs
  - New materials for selected removal of smoke constituents or combustion control
- Both Internal and External Research

PM3001168022

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Other PM Activities Toward the Future
Philip Morris External Research Program

Purpose: Support the highest quality research that:

- Contributes to our fundamental scientific knowledge,
- Helps address the concerns of the public health community regarding cigarette smoking, and
- Enables Philip Morris to continue its pursuit of product modification(s) or new product design(s) that might reduce the health risks of smoking.

Focus:

- Exposure / Biomarkers / Dosimetry
  - Measures of exposure (including methodologies)
  - Measures of biological effects
- Epidemiological Research
  - Cancer
  - Cardiovascular diseases
  - Respiratory diseases
  - Reproductive, maternal and placental effects
  - Combination designs of some or all of the above
  - Exposure, biomarkers, and potential mechanisms
- Clinical and Model Systems Research, including Validation, and Assays
  - Cancer
  - Cardiovascular diseases
  - Respiratory diseases
  - Reproductive, maternal, and placental effects
  - Relevant smoke constituents related to mechanisms
- Mechanistic Research
  - Molecular reactions related to cell regulation
  - Cellular processes
  - Disease mechanisms
- Tobacco Smoke and Smoking Behavior
  - Biochemical and molecular mechanisms
  - Nicotine
  - Other smoke constituents

Handout provided:
- "Analytical Determination of Nicotine" book
- Philip Morris External Research Program - Request For Application

PM3001168023

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Other PM Activities Toward the Future
2000 Philip Morris Publications & Presentations - RD&E*

- 9 Publications
- 60 New manuscripts submissions planned
- 81 Presentations made
- Representative areas:
  - Ignition propensity
  - Cigarette design and function
  - Metallurgy
  - Nicotine
  - Ingredients
  - Aerosol physics
  - Toxicology
  - Electrically heated cigarettes
  - Smoke chemistry
  - Indoor air
  - Nitrosamines

*Data as of October 9, 2000

PM3001168024

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001

Summary

- Harm Reduction Must be Properly Evaluated
  - Exposure is an important part, in addition to hazard
- PM Takes the Pursuit of Harm Reduction as a Priority
  - Is Pursuing Harm Reduction in a Responsible Way
  - Welcomes the involvement of the public health community
- Quitting Is the Best Way to Reduce Risk
- If Adults Who Choose to Smoke Do Not Switch to a Reduced Harm Product, They Do Not Benefit
- PM Will Be Glad to Provide Support to, and Receive Support from, This WHO Committee
  - Some areas of cigarette relevant expertise: toxicology, pathology, epidemiology, statistics, molecular biology, biochemistry, analytical chemistry
  - RD&E staff of approximately 600
  - Toxicology testing laboratories (INBIFO and CRC) with staff of approximately 170
  - WSA staff dedicated to smoking and health concerns

PM3001168025

Source: https://www.industrydocuments.ucsf.edu/docs/mfgk0001